UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/498,537	02/04/00	BUELOW J	ROBU.003.01U

HM12/0622

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EXAMINER	
WOITACH, J	
ART UNIT	**PAPER NUMBER**
1632	15

DATE MAILED: 06/22/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/498,537	Applicant(s) BUELOW, JENULRICH	
	Examiner Joseph Woitach	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-12,14-19 and 26-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-12,14-19 and 26-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

Please note that the Examiner of record and art unit has changed. The Examiner of record is now **Joseph Woitach** and the group art unit is now **1632**.

This application filed February 4, 2000, is a continuation in part of applications: 60/118,810, filed February 5, 1999; 60/134,674, filed May 18, 1999; and 60/131,398, filed April 28, 1999.

Applicants amendment file April 13, 2001, paper number 14, has been received and entered. Claims 3, 13 and 20-25 have been canceled. Claims 1, 2, 4-8, 11, 12, 14-19, 26, 27 and 30-32 have been amended. Claims 33-44 have been added. Claims 1, 2, 4-12, 14-19 and 26-44 are pending and currently under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11, 12, 14-18 and 26-32 stand rejected and claims 43 and 44 are newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of generating a transgenic rabbit, comprising the use of art accepted nuclear transfer technology wherein the nuclear transfer unit is generated by homologous recombination of a polynucleotide

sequence which encodes human immunoglobulin heavy chain or a polynucleotide sequence which encodes human immunoglobulin light chain, and said rabbit generated by said method, does not reasonably provide enablement for methods of making all transgenic animals which generate antibody diversity by gene conversion. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

In an effort to advance prosecution, Applicants have amended the claims 11, 12, 14-18, 26-28 and 30-32, and added claims 43 and 44, to be drawn to better characterize the transgenic non-human animal as one "which generates antibody diversity predominantly by gene conversion." Applicants argue that the specification provides adequate guidance on how to generate a transgenic non-human animal which generates antibody diversity predominantly by gene conversion, and specifically point to the specification at page 5, lines 25-27 and pages 6-9 in support of an enabling disclosure. In addition, Applicants note that the specification exemplifies the procedure and provides a working example in the generation of a transgenic rabbit (specification, pages 11-12). See Applicant's amendment, page 10-11. Applicant's arguments have been fully considered but not found persuasive.

As noted in the previous office action, the present specification provides specific guidance for the production of a transgenic rabbit through nuclear transfer technology, however relies in great part on the state of nuclear transfer technology as known or taught in the art. As discussed in Wall, Houdebine, Hammer *et al.* Ebert *et al.*, Mullins *et al.* and Kappel *et al.*, the state of the

art of generating transgenic animals is unpredictable, in particular the production of one transgenic animal species is not predictive of the ability to generate a similar transgenic animal in a second different species (see previous office action, pages 5-8). The specification provides one working example of a transgenic rabbit generated by nuclear transfer technology. Though the specific polynucleotide sequences used to generate the nuclear transfer unit used to generate said transgenic rabbit are not taught in the instant specification, exemplification of a transgenic rabbit which can generate humanized antibodies to HBsAg when immunized indicates that one of skill in the art of nuclear transfer technology using the guidance of the instant specification could generate a similar transgenic rabbit.

Applicants have amended the claims to encompass transgenic non-human animals "which generates antibody diversity predominantly by gene conversion", and while Examiner would concede that art recognizes that rabbits, pigs, sheep and cattle predominantly use gene conversion for the generation of antibodies, Applicants have not indicated in the present specification teachings which overcome the unpredictable nature generating any transgenic animal. Because the specification relies on the state of the art for the production of other transgenic non-human animals besides a transgenic rabbit, the generation of other species of non-human animals is subject to the same art recognized obstacles of transgenics taught by Wall, Houdebine, Hammer *et al.* Ebert *et al.*, Mullins *et al.* and Kappel *et al.*, and the generation of any non-human animal in light of only one working example would be considered unpredictable. In addition, as pointed out in the previous office action, the specification provides only general guidance to the

polynucleotide sequences which should be used, and does not provide any specific guidance to which specific polynucleotide sequences used to generate the transgenic rabbit. Absent of adequate guidance on how to generate the proper polynucleotide constructs for the generation of the proper nuclear transfer units for other species of non-human animals besides the rabbit, one of skill in the art would not know how overcome the unpredictability associated with the art of transgenics to practice the full breadth of the method as claimed.

Thus, in view of the lack of guidance, working examples, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to use the invention as claimed, and therefore, the rejection is maintained.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 4-12, 14-19 and 26-44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

Claim 1 is unclear in the recitation of 'immunoglobulin protein molecules comprised of at least a portion of a human immunoglobulin protein polypeptide sequence' because it is not clear if that each specific immunoglobulin protein molecule contains a human immunoglobulin sequence

or that the composition of molecules contains a human immunoglobulin, and thus would be anticipated by a composition comprising a mixture of human and non-human antibodies.

Claim 26 is unclear and confusing because it recites a method of producing a transgenic non-human animal, however the method steps include the production of two neonates. It is unclear why two different transgenic animals are produced by a single method in different steps.

Claim 27 is unclear in the recitation of 'breeding mature mutate neonates' because the preceding method steps produce only one neonate, and in addition, there are no steps wherein the mutated neonate is matured to be used in the final method step.

Claims 43 and 44 are unclear in the recitation of 'by genetically altering a cell nucleus of the animal' because it is not clear if the mutation is done *in vivo* or in an isolated cell, and if done in vivo, there are no method steps wherein the cell and nucleus of said cell are extracted form the animal. In addition, the final step requires that the animal produced be tested to determine if the method as practiced resulted in the animal recited in the preamble, however there are not steps to practice this portion of the claim, and it is unclear how one would practice or achieve this final step.

Dependent claims not specifically recited in the above rejections are included in the rejection because they fail to further clarify the basis of the rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-10 stand rejected and claims 19 and 33-42 are newly rejected under 35 U.S.C. 102(e) as being anticipated by Lonberg *et al.* (US Patent 5,874,299).

Applicants indicate that the claims have been amended to recite a polyclonal antisera composition of a transgenic non-human animal "which generates antibody diversity predominantly by gene conversion." Applicants argue that the polyclonal antisera taught by Lonberg *et al.*, which is generated in transgenic mice (which is generated by gene rearrangement), is distinct from the antisera as instantly claimed (which is generated by gene conversion). See Applicants amendment, page 13. Applicants amendment has been fully considered but not found persuasive.

Examiner agrees that the mice and rabbits generate antibodies by different molecular mechanism, however the resulting antibody is the same. As noted in the previous office action, patentability of a product-by-process claim is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for making it which is recited in the claims. *In re Thorpe*, 227 USPQ 964 (Fed. Cir. 1985). Applicants assert that the antibodies

generated are distinct yet have failed to indicate how the polyclonal antibodies differ or are distinct. Lonberg *et al.* teach the creation of transgenic mice which include the polynucleotide sequences which encode both the heavy and light immunoglobulin transgenes. Lonberg *et al.* propose by introducing the repertoire of unrearranged transgenes, that upon contact with an antigen induction and production of a heterologous antibody will be produced (for example in column 4). Further, at the time of filing the art recognized that even similar molecular mechanisms may be involved in the generation of the production of immunoglobulins in mice and rabbits (Blanden *et al.* (Imm. and Cell Biol, 1998)). Therefore, absent to evidence to the contrary, the polyclonal antisera taught by Lonberg *et al.* anticipates the antisera composition instantly claimed, and the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 11-18 and 26-32 stand rejected and claims 43 and 44 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Lonberg *et al.* taken with Brem *et al.* and Stice *et al.*

Applicants argue that Lonberg *et al.* does not teach or suggest any means for making transgenic animals which generate antibody diversity by gene conversion, only methods for use of transgenic mice. Further, Applicants argue that Lonberg *et al.* teach making human monoclonal antibodies (column 3; lines 20-40), and one of skill in the art would have not been motivated by the teaching of Lonberg *et al.* to make non-human transgenic animals which generate antibody diversity by gene conversion. In addition, Applicants argue that Brem *et al.* teach the production transgenic animal encoding a single rearranged antibody, and Stice *et al.* only discuss the production of transgenic animals in general. Applicants argue that one of skill in the art would not have been motivated to combine cited prior art references, citing *In re Vaeck* for support of their arguments. See Applicants amendment, pages 15-16. Applicants arguments have been fully considered, but not found persuasive.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Examiner agrees that Lonberg *et al.* teach that the described methodology can be used to generate monoclonal antibodies, however, other embodiments taught by Lonberg *et al.* are drawn to the production of heterologous antibodies (column 3; lines 40-57, in

Background following applicants cited portion). Further, in the Summary of the invention, Lonberg *et al.* clearly teach that transgene introduced can be unrearranged light and heavy immunological transgenes which can be inserted into the genome of an animal such that segments from the transgene can rearrange with endogenous genomic sequences (column 4; lines 15-67 and column 5; lines 5-55). Lonberg *et al.* teach specific human immunoglobulin polynucleotide sequences which can be used to create such transgenes and methods of obtaining additional sequences. Lonberg *et al.* teach that the methodology can be used to generate any non-human animal and provide working examples of several transgenic mouse lines. The teaching of Lonberg *et al.* clearly indicates that the methodologies applied to generating the working examples can be used to generate transgenic animals other than transgenic mice. Brem *et al.* and Stice *et al.* both teach specific methodologies in generating transgenic non-murine animals and serve to illustrate the state of the art of transgenics and animal cloning at the time of filing. In view of the level of skill in the art for creating transgenic animals as illustrated by Stice *et al.* and in particular, for the creation of heterologous antibodies as taught by Brem *et al.*, it would have been *prima facie* obvious to one of ordinary skill in the art to combine the detailed teachings of Lonberg *et al.* to create a transgenic rabbit to produce heterologous antibodies as taught by Brem *et al.* with methodologies known and summarized in the art by Stice *et al.* As noted by Brem *et al.* one would be motivated to produce other transgenic non-human mammals such as the rabbit to generate animals that are resistant to various diseases or that generate new heterologous antibodies using said transgenic animal (column 5; lines 1-35).

Thus, for the reasons above and of record, the claimed invention as a whole would have been *prima facie* obvious, absent of evidence to the contrary, and therefore, the rejection is maintained.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach, whose telephone number is (703) 305-3732. The examiner can normally be reached on Monday through Friday from 8:00 to 4:30 (Eastern time).

If attempts to reach the examine by telephone are unsuccessful, the examiner's supervisor, Karen M. Hauda, can be reached on (703) 305-6608. The fax number for group 1600 is (703)308-4724.

An inquiry of a general nature or relating to the status of the application should be directed to Kay Pickney whose telephone number is (703) 305-3553.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703)308-4242 and (703)305-3014.

Joseph T. Woitach

JILL D. MARTIN
PRIMARY EXAMINER